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10/509,694	09/26/2005	Daniel F Hanley	58719(71699)	2172

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EXAMINER	
WEBB, WALTER E	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,694	HANLEY ET AL.	
	Examiner	Art Unit	
	Walter E. Webb	4133	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

The disclosure is objected to because of the following informalities: in claim 2, "intraventriclar" is misspelled.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of blood clots, does not reasonably provide enablement for prevention of blood clots. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;

2) the breadth of the claims;

3) the predictability or unpredictability of the art;

4) the amount of direction or guidance presented;

5) the presence or absence of working examples;

6) the quantity of experimentation necessary;

7) the state of the prior art; and,

8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

Factors 1 and 2: Applicant's invention is drawn to a method of treating or preventing extravascular hematoma or blood clots in a subject by administering a therapeutically effective amount of a thrombolytic agent.

Factors 3 and 7: In particular, one skilled in the art could not practice the presently claimed subject matter without undue experimentation because the artisan would not accept on its face that the prevention of blood clots, which exhibited some sensitivity to thrombolytic agents, could be effectively achieved by the administration of the claimed active agents. The artisan would have only accepted that the treatment of blood clots could be achieved, rather than that such an agent(s) could have been used to prevent blood clots.

As set forth in *In re Marzocchi* et al., 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112 unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support; assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling."

Factors 4: Applicant disclosed guidance in the form of clinical analysis and the efficacy of the treatment of clots by t-PA and urokinase. Still, further guidance is needed with regard to prevention. To enable the artisan to reasonably predict that Applicant's composition can prevent blood clots, Applicant should set forth a protocol or guidance as to how prevention of these clinical symptoms could be achieved. Applicant's disclosure is inadequate as to directing or guiding how the proposed agents can be employed to accomplish such objectives in a predictable manner.

Factors 5: The specification at pages 21-34 provides examples of treating blood clots clinically with the claimed agents. While the present claims encompass preventing blood clots, Applicant's data merely establishes methods for treating blood clots. No data has been provided, or reasonable scientific basis exists, for treating such results as a prevention of blood clots.

Administration of urokinase and t-PA are not fail-safe agents for the treatment of blood clots, and therefore would clearly not be able to prevent blood clots. In this regard Naff et al, (*infra*) is cited. The Naff reference states in their Results section at page 616 that patients receiving t-PA treatment experienced an increase in clot volume in the initial 48 hour treatment.

Given that the art recognized that a thrombolytic agent could fail in the resolution of clots, one of ordinary skill in the art would not accept on its face Applicant's statement that prevention of blood clots could be achieved.

The Examiner acknowledges that the Office does not require the presence of working examples to be present in the disclosure of the invention (see MPEP §2164.02). However, in light of the state of the art, which recognizes the unpredictable nature of treating blood clots, there is no apparent disclosure to support the contention that blood clots can be prevented by simply administering, by any method, the claimed thrombolytic agents, since the present specification fails to enable one of ordinary skill in the art to practice the entirety of the presently claimed invention.

Factor 6: The burden of preventing blood clots with the claimed thrombolytic agents is much greater than that of treating blood clots, with the claimed thrombolytic agents. Since the present specification would not enable the artisan to prevent blood clots, a clear burden of undue experimentation would be placed upon the artisan in order to practice the full scope of the presently claimed invention.

Factor 8: In view of the discussion of each of the preceding seven factors, the level of skill in this art is high and is at least that of a medical doctor with several years of experience in the art.

Summary

As the discussion of the above 8 factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the artisan with a reasonable expectation that preventing blood clots with the claimed thrombolytic agents could be achieved. In order to actually achieve such an objective, it is clear from the discussion above that the artisan could not rely on Applicant's disclosure as required by 35 U.S.C. § 112, first paragraph. Given that the art fails to recognize, and Applicant as failed to demonstrate, via direct evidence or sound reasoning, that blood clots can be prevented with the claimed thrombolytic agents, the artisan would be faced with the impermissible burden of undue experimentation in order to practice this embodiment of the claimed invention. Accordingly, claims 1-20 are deemed properly rejected.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 7, 9-15, and 18-20 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6, 7, 10, and 20 are indefinite because of these abbreviations: t-PA or rt-PA (claim 6 and 20), EVD (claim 7), and CT (claim 10). The abbreviations should be spelled out first to avoid confusion.

Claims 11-15 are indefinite due to unclarity of whether "at least" or "about" controls the metes and bounds of the claim limitations in the instant claims.

Claim 9 is also indefinite due to the unclarity of whether "between" or "about" controls the metes and bounds of the claim limitations in the instant claim.

The term "units" in claims 18 and 19 is a relative term, which renders the claim indefinite. The term "units" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 and 6-10 are rejected under 35 U.S.C. 102(a) as being anticipated by Naff et al., (Neurosurgery 2001).

Applicant's invention is drawn to a method of treating or preventing extravascular hematoma or blood clot in a subject by administering a therapeutically effective amount of a thrombolytic agent (claim1), where the blood clot is associated with intraventricular hemorrhage (claim 2), intracerebral hemorrhage (claim 3), or subarachnoid hemorrhage (claim 4). The thrombolytic agent is t-PA or rt-PA (claim 6) and administered in conjunction with EVD (External Ventricular Drainage) (claim 7). The thrombolytic agent is administered between about 12-24 hours or 24-48 hours after diagnosis of Intraventricular hemorrhage, intracerebral hemorrhage, and/or subarachnoid hemorrhage (claims 8 and 9). Further, CT scans are performed at intervals of about 6-24 hours to monitor blood clot size and/or whether bleeding is occurring (claim 10).

Naff et al. teach a method of treating blood clots in patients where the blood clots are associated with Intraventricular hemorrhage, intracerebral hemorrhage, and/or subarachnoid hemorrhage. (See Results at pg. 616.) Treatment also involved external ventricular drainage (EVD). (See ibid.) Computed Tomography (CT) scans were used to monitor clot size. (See Table 1. at pg. 615.) Patient 3 was monitored at an interval of 8.6 and 24.5 hours. (See ibid.) The thrombolytic agent used was t-PA (tissue-plasminogen). (See Peripheral versus CSF thrombolysis at pg. 617.) Naff et al. teach administration of thrombolytic agents within the first 24-48 hours after hemorrhage diagnosis. (See Implications for CSF thrombolytic therapy.)

Claims 1-5, 7, 10, 15 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Wright et al., (Journal of Stroke and Cerebrovascular Disease 2001).

Applicant additionally claims a method of claim 1 where the thrombolytic agent is urokinase (claim 5), and is administered at least about every 12 hours (claim 15), wherein the urokinase is administered in doses of about 5000-50,000 units (claim 18).

Wright et al. teach administration of urokinase to a patient with Intraventricular hemorrhage at a dose of 25,000 U every 12 hours (see Abstract at pg. 23). The patient received daily CT scans to monitor the bleeding (see Case Report at pg. 24), which satisfies the 6-24 hr interval limitation of claim 10. The patient was also treated with EVD (see third paragraph of pg. 23, and Discussion, last paragraph, at pg. 25). The patient also experienced thalamic hemorrhage, a form of intracranial hemorrhage, and intracranial pressure, which is an indication of subarachnoid hemorrhage (see third paragraph of pg. 23).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naff et al. (*supra*) in view of Wright et al., (*supra*) as applied to claims 1-10, 15 and 18 above.

Naff et al. teach administration of t-PA in the treatment of blood clots where patients have been diagnosed with Intraventricular hemorrhage, intracerebral hemorrhage, and/or subarachnoid hemorrhage (see discussion above). Clot volume was measured as a percentage of initial blood clot volume over a 12-day period (see Results, Figure 1, at pg. 616).

Naff et al. does not teach administration of urokinase, administration of thrombolytic agent at least every 4, 6, 8, 10, or 12 hours. They do not explicitly teach stopping administration of the thrombolytic agent when the clot size is about 80% of its original size, at about 3 days, or administering doses of urokinase at about 5000-50,000 units, or 12,500 units, or administering t-PA or rt-PA at a dose of about 0.1-10 mg.

Wright et al. teach a method of administering urokinase to a patient to treat blood clots as a result of intraventricular hemorrhage, where the patient was administered urokinase at 25,000 U every 12 hours (see discussion above). They also teach future use of rTPA since urokinase "is now not clinically available." (See Discussion at pg. 25, right column bottom of 2nd full paragraph.)

It would have been obvious to a person having ordinary skill in the art at the time of Applicant's invention to administer the throbolytic agents of Naff and Wright as claimed to treat blood clots since the adjustment of particular conventional working conditions of these thrombolytic agents (e.g., determining result effective amounts of the ingredients beneficially taught by the cited references, especially within the broad ranges instantly claimed), is deemed merely a matter of judicious selection and routine optimization, which is well within the purview of the skilled artisan. Accordingly, this type of modification would have been well within the purview of the skilled artisan and no more than an effort to optimize results.

Furthermore, it is also within the purview of the artisan to stop administration of the thrombolytic agent when the blood clot is about 80% of its original size at about 3 days (claims 16 and 17) since Naff et al. teach that the thrombolytic system is saturated at 24-48 hours where clot resolution would not accelerate. (See Implications for CSF thrombolytic therapy at pg. 618.) It is also at about the 3-day period where the clot size is about 80% of its original size (see Results, Figure 1, at pg. 616). "[A] person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of

innovation but of ordinary skill and common sense." KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385, 1390.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Seifert et al., (Neurosurgery 1989), which details the use of rtPA in the reduction of cerebral vasospasm after subarachnoid hemorrhage.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Walter E. Webb whose telephone number is (571) 270-3287. The examiner can normally be reached on 9:00am-5:00pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

WW

11/13/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER